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Case report

A new *ENG* mutation in a Japanese family with hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformations

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ABSTRACT

We present a case series of four siblings with hereditary hemorrhagic telangiectasia (HHT) and pulmonary arteriovenous malformations (PAVM). The patients' mother has HHT. Case 1: A 22-year-old man developed dyspnea and epistaxis. CT revealed a large PAVM, treated by segmentectomy. Case 2: A 27-year-old woman developed epistaxis and dyspnea. CT revealed three PAVMs, treated by partial resection. Case 3: A 20-year-old woman developed dyspnea. CT revealed multiple PAVMs, treated with endovascular occlusion of the largest one. Case 4: A 12-year-old woman developed epistaxis. CT revealed multiple PAVMs, observed without treatment. Genetic testing identified a new mutation, ENG c.1517T > C (p.Leu506Pro), in all patients and their mother. We suspect that HHT in these patients may be associated with this ENG mutation.

1. Introduction

Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu disease, is an autosomal dominant disease characterized by mucocutaneous telangiectasias, epistaxis and visceral arteriovenous malformations (AVM) most commonly found in the lungs, liver, and brain [1,2]. In Japan, the incidence of HHT is estimated to be 1:5000 to 1:8000 [3], which is similar to reports from other countries [4–6]. HHT is clinically diagnosed based on the Curaçao criteria: 1) an affected first-degree family member, 2) recurrent epistaxis, 3) multiple telangiectasia along the mucocutaneous surface, and 4) arteriovenous malformations in major organs. The diagnosis is considered “confirmed” in an individual with at least three, and “suspected” with two of the above features [4]. These features progress with age and pulmonary arteriovenous malformation (PAVM) development is thought to be complete by the end of puberty [7,8].

Recently, genetic research has demonstrated that heterozygous mutations including *ENG*, *AVCRL1*, and rarely *SMAD4* are causative genes of HHT. There are at least two other unidentified genes that can cause HHT [7,8]. The majority of HHT patients have mutations in *ENG*, encoding endoglin, or *ACVRL1*, encoding activin receptor like kinase. These genes are associated with the transforming growth factor (TGF)-β superfamily signaling pathway, which is important for maintaining vascular integrity [5–7]. HHT with *ENG* mutation is characterized by a high incidence of PAVMs and cerebral AVMs [9], whereas HHT with *ACVRL1* is associated with hepatic AVMs. It is thought that clinical profiles have some correlation with the genotype.

Here we report four patients with familial HHT with PAVM associated with a new *ENG* mutation.

2. Case reports

In August 2015, a 48-year-old woman with HHT visited Sapporo Medical University Hospital for clinical genetic counseling with her four children, a son (Case 1) and three daughters (Case 2, 3, and 4). She had undergone left lower lobe lobectomy of a PAVM in the past. After

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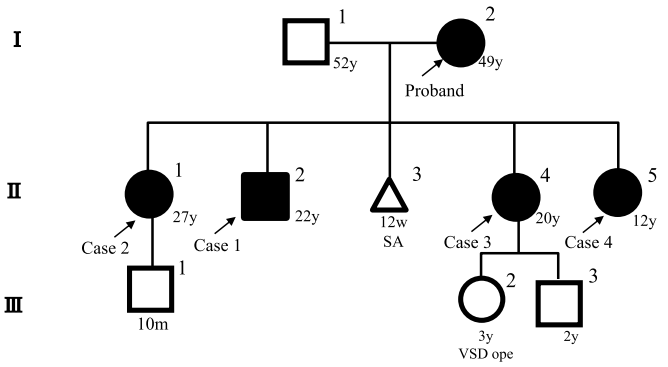

Fig. 1. Pedigree of family with hereditary hemorrhagic telangiectasia with genetic mutation. Filled and open symbols means affected and unaffected individuals, respectively. Genetic testing was performed on individuals represented by filled symbols. SA; spontaneous abortion, VSD; ventricular septal defect.

careful investigation of the family history, we suspected they might have HHT and we recommended genetic testing of the four children. They underwent examination at Kushiro City General Hospital and were treated at Sapporo Medical University Hospital.

Case 1, 2, and 4 were clinically diagnosed as HHT with PAVM, and Case 3 was diagnosed with suspected HHT with PAVM. The family pedigree is presented in Fig. 1. Genetic testing of the mother and four siblings identified a new mutation of endoglin gene, ENG c.1517T > C (p.Leu506Pro) (RefSeq accession number NM_001114753.1) (Fig. 2). Therefore, we made a final diagnosis of familial HHT associated with the ENG mutation. The four siblings are summarized in Table 1 and their cases are described below.

2.1. Case 1

A 22-year-old man complained of dyspnea and recurrent epistaxis. He had a history of bronchial asthma, attention deficit hyperactivity disorder, learning disabilities and dysgraphia. He had telangiectasias in his fingers and lips, clubbing, and expiratory wheezing. A vascular murmur (bruit) was auscultated in his right lower back. Arterial blood gas showed a partial pressure of arterial oxygen (PaO_2) of 51.4 mmHg and arterial oxygen saturation (SpO_2) of 83% on room air. Blood testing revealed a hemoglobin level of 20 g/dl. Chest radiograph showed a large nodule in the right lower lung field with enlarged vessels. Chest CT revealed a PAVM located in the right segment (S) 10, which was 60 mm in diameter (Fig. 3). The PAVM was characterized as a simple type with a feeding artery of 10 mm and a draining vein of 13 mm in diameter. Perfusion scintigraphy showed a right-to-left shunt fraction of 29.7%. Brain magnetic resonance imaging (MRI) and abdominal CT were normal. A gastrointestinal endoscopy did not show any vascular lesions.

Surgical treatment was indicated because the PAVM was unilateral and peripherally located. Transcatheter embolization of the feeding artery was thought to be difficult because the PAVM was very large and both the feeding artery and the draining vein were thick. There was a higher risk of paradoxical embolization such as migration of occlusive devices or blood clots. Therefore, we treated the PAVM by segmentectomy with video-assisted thoracoscopic surgery (VATS). After the surgery, the shunt fraction decreased to 14.2% and SpO_2 rose to 94% on room air.

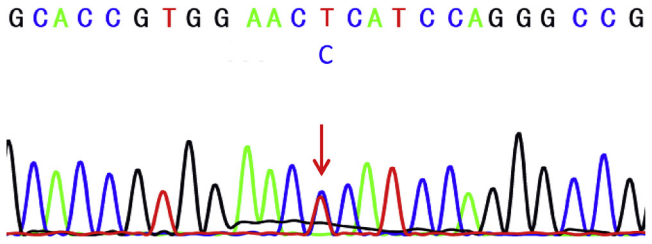

Fig. 2. DNA sequencing results. All patients and their mother exhibited a new ENG mutation (NM_001114753.1: c. 1517T > C, NP_001108225.1: p. Leu506Pro).

Chest CT taken 16 months post-operatively revealed a new asymptomatic small PAVM, 3 mm in diameter, in the right upper lobe. As the feeding artery was less than 3 mm in diameter and the patient had no symptoms, we recommended careful observation.

2.2. Case 2

A 27-year-old woman complained of recurrent epistaxis and mild dyspnea on exertion. She had history of bronchial asthma and irritable bowel syndrome. She had telangiectasias in fingers and lips. Auscultation was normal. Arterial blood gas analysis showed a PaO_2 of 95.5 mmHg and SpO_2 of 98% on room air. Chest CT revealed multiple PAVMs in the right S4, the right S6 and the left S4 (Fig. 4) and they were 5 mm, 7 mm and 5 mm in size, respectively. They were of the simple type and supplied by feeding arteries of 3–4 mm in diameter. A brain MRI, an abdominal CT and a gastrointestinal endoscopy showed no abnormal finding. Perfusion scintigraphy revealed a right to left shunt fraction of 6.8%. These clinical features satisfied the diagnostic criteria for HHT.

Incidentally, she developed an allergic reaction to CT contrast, characterized by dyspnea and urticaria. Given that contrast is also necessary for transcatheter embolization and due to the risk of anaphylaxis and cardio-pulmonary failure, we performed surgical removal of three PAVMs via VATS instead. Moreover, three additional PAVMs were discovered on the surface of the visceral pleura of the right S3, S8 and S10 by direct observation during the operation. These PAVMs on the pleural surface were excised by electroablation using the SOFT COAG electrosurgical output system.

2.3. Case 3

A 20-year-old woman complained of dyspnea on exertion. She had history of idiopathic thrombocytopenic purpura and bronchial asthma as well as autistic spectrum disorder, depression, and intellectual impairment. She had given birth twice. Mucosal and skin examinations showed no abnormality. Auscultation was normal. Arterial blood gas demonstrated a PaO_2 of 93.8 mmHg and a SpO_2 of 95% on room air. Chest radiograph showed well-defined nodular lesions in the right lower lung field. Chest CT revealed multiple PAVMs in both lungs (Fig. 5). The largest one was 18 mm in diameter, it was located in right S10, and had two feeding pulmonary arteries of 3 and 5 mm in diameter. Perfusion scintigraphy revealed a right-to-left shunt fraction of 8.5%. Brain MRI and abdominal CT were normal. Although clinical features did not satisfy the Curaçao criteria, genetic testing confirmed the diagnosis. Given her multiple PAVMs, we selected to treat the largest PAVM in right S10 by transcatheter embolization using vascular coils.

2.4. Case 4

A 12-year-old woman complained of recurrent epistaxis. She had history of mental and adjustment disorders. Physical examination revealed telangiectasias in fingers and lips. Chest CT revealed small diffuse PAVMs with a feeding artery of less than 3 mm in diameter in both lungs (Fig. 6). Enhanced abdominal CT showed no abnormal finding. Due of her psychological instability, she was unable to undergo brain MRI. Since the size of the PAVMs was small and the diameter of the blood vessel was 3 mm or less, we managed her conservatively. Laser ablation treatment for nasal mucosal telangiectasia reduced the